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Enzymatic Desymmetrisation of Prochiral Phosphines and Phosphine *P*-Sulfides as a Route to *P*-Chiral Catalysts

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Abstract: The enzyme-catalyzed monoacetylation of prochiral bis (2-hydroxymethylphenyl)methyl phosphine and bis (2-hydroxymethylphenyl)phenylphosphine and their *P*-sulfides gave, in one single step, as a result of desymmetrisation, the corresponding monoacetates in moderate yields and with an enantiomeric excess of 16 to 98%, depending on the substrate structure and enzyme applied. The absolute configurations of the selected products were determined by a chemical correlation. This led to the conclusion that, in the case of phosphines, phosphine oxides and phosphine sulfides enzymes preferentially produce compounds of the same spatial arrangement. The new compounds obtained will be transformed into chiral catalysts/ligands.

Keywords: biotransformations; configuration determination; desymmetrisation; enzyme catalysis; phosphorus compounds

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1. Introduction

Since the pioneering times of the mid-1970s, when the first practical and generally applicable methods in asymmetric synthesis [1] were developed, there has been a tremendous growth in this research field.

One of the fundamental research goals in modern chemistry is the development of efficient and selective procedures to access organic compounds. Among all the methodologies developed to date, catalysis offers an efficient and economical approach to enantiomerically pure substances. In particular, organocatalysis, transition metal catalysis and enzymes, and biotechnology methods are in high demand due to their application in stereoselective carbon–hydrogen, carbon–carbon or carbon–heteroatom bond formations.

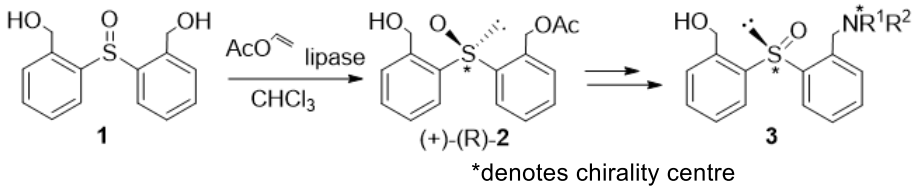
Among the commonly used catalysts, there is a substantial number of hetero-organic compounds, especially organic phosphorus and sulfur compounds. Concerning the former ones, there are mainly phosphines and phosphine oxides [2], whose synthesis requires the application of various methodologies. Among them, the desymmetrisation of prochiral phosphorus substrates seems particularly interesting. Such transformations were performed mainly in a chemical manner, using chiral catalysts (for some recent results see [3,4]). There are only a few examples of the use of enzymes as catalysts, such as desymmetrisation [5–8], three of which came from our laboratory [5,7,8] (vide infra).

The chiral sulfur derivatives that were applied in asymmetric catalysis are variously functionalized sulfinyl compounds, sulfoximines and others (for a recent overview on the use of *S*-chiral sulfur ligands/catalysts in asymmetric synthesis, see [9]).

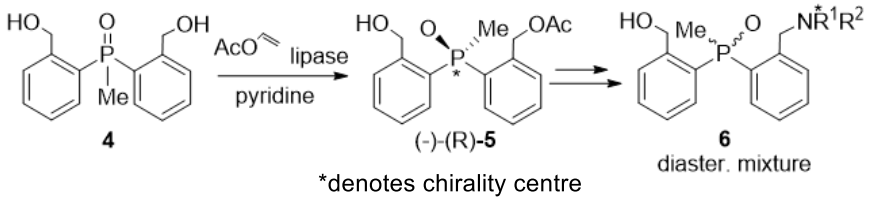
Searching for new chiral catalysts, we synthesized some time ago a series of organosulfur chiral compounds **3**, containing a stereogenic sulfinyl moiety, an enantiomeric amine fragment and the hydroxyl group (Scheme 1) [10,11]. They proved to be excellent catalysts in a variety of reactions of asymmetric synthesis [9,12].

Following these positive results, we decided to synthesize catalysts in which the stereogenic sulfinyl moiety was replaced by a stereogenic phosphorus-containing group.

In the first approach, attempts were made at the synthesis of the phosphinyl (P = O) analogues. We synthesized the enantiomerically pure (2-acetoxymethylphenyl)(2′-hydroxymethylphenyl)phosphine oxide **5**, which was planned to be a precursor of the desired ligands **6** (Scheme 2).



Scheme 1. Synthesis of chiral tridentate sulfinyl catalysts.



Scheme 2. Synthesis of chiral phosphine oxides as substrates for potential tridentate ligands.

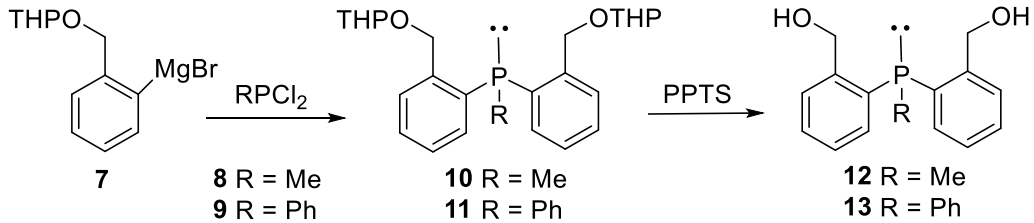
The initial steps involving the enzymatic desymmetrisation of **4** (Scheme 2) were fully successful [8]. In all cases, the catalyst precursor **5** was obtained in high yields and with *ee*s up to 99.5%. Unexpectedly, attempts to replace the hydroxyl group with an enantiomerically pure chiral amine moiety via the mesylation of enantiomerically pure **5** always led to mixtures of diastereomers (which was not the case for the corresponding sulfinyl analogs **2**), which means that racemization must have taken place at one of the stages of the synthesis. The partial racemization of enantiomeric precursor **5** ultimately led to the formation of inseparable diastereomeric mixtures of the desired ligands **6** [13]. Moreover, the latter proved to be totally ineffective as catalysts for the several reactions of asymmetric synthesis [14].

Later, we found that the phosphinyl group (P = O) is responsible for both negative features of ligands **6** [13,14]. Therefore, we decided to use, instead of the phosphinyl substrates, the corresponding phosphines **12**, **13** and sulfides **22**, **23**, in the hope of avoiding the above problems.

2. Results and Discussion

2.1. Synthesis of Bis (2-hydroxymethylphenyl)phosphines **12** *and* **13**

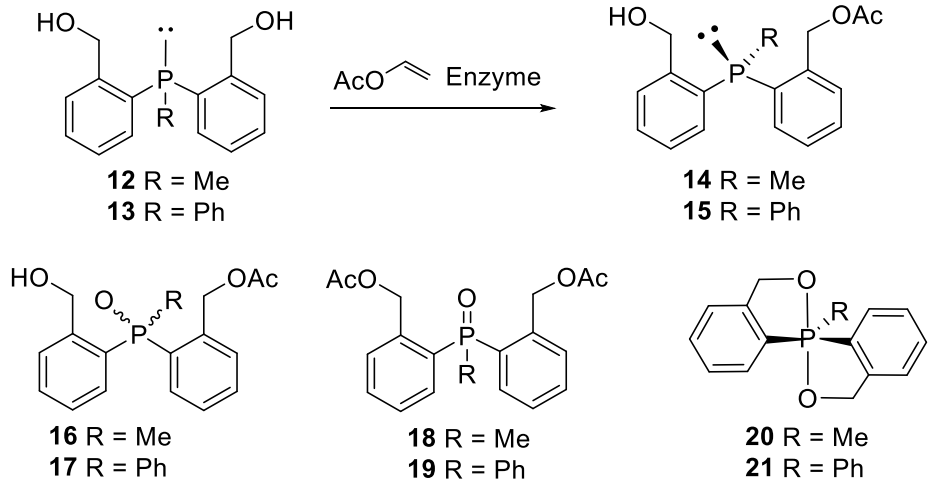
The syntheses of starting phosphines **12** and **13** were based on the reactions of *o*-tetrahydropyranyloxymethylphenylmagnesium bromide (Mg-THPBB) **7** with the appropriate dichlorophosphines **8** and **9**. Thus, the synthesis of bis (2-hydroxymethylphenyl)methyl phosphine **12** was achieved by the reaction of dichloro (methyl) phosphine **8** with Mg-THPBB **7** to give **10**, which was then treated with pyridinium *p*-toluenesulfonate (PPTS) to remove the THP protecting group. In turn, the synthesis of bis (2-hydroxymethylphenyl) phenylphosphine **13** was accomplished in a similar way, starting from dichloro (phenyl) phosphine and treatment of the resulting **11** with PPTS [8] (Scheme 3).



Scheme 3. Synthesis of bis (2-hydroxymethylphenyl)phosphines **12** and **13**.

2.2. Desymmetrisation of Bis (2-hydroxymethylphenyl)phosphines **12** *and* **13**

Due to the fact that in our laboratory we have successfully used enzymes for the synthesis of non-racemic hetero-organic compounds, particularly those containing stereogenic phosphorus and sulfur atoms, we decided to use also in this case such a procedure for desymmetrisation of the appropriate substrates. Thus, prochiral phosphines **12** and **13** were subjected to asymmetric acetylation with an excess of vinyl acetate in various solvents at 30 °C, using selected enzymes as biocatalysts (Scheme 4).



Scheme 4. Desymmetrisation of bis (2-hydroxiymethylphenyl)phosphines **12** and **13**.

The reactions were monitored by ^{31}P NMR. After completion, the enzymes were filtered off, the solvent and excess of vinyl acetate were evaporated to leave the residue, which, in addition to the desired enantiomerically enriched monoacetates **14** and **15**, contained some byproducts. These were the corresponding oxidized derivatives **16** and **17**, diacetates **18** and **19** and phosphoranes **20** and **21**, whose formation proved inevitable in spite of all the undertaken protection from air (as shown in Scheme 4)

The residue was separated via column chromatography and the results are collected in Table 1. The inspection of Table 1 clearly shows that the products exhibiting the highest enantiomeric excess were obtained using CAL-B as the biocatalyst and toluene as the solvent in acetylation of diol **12** and CAL-B as the biocatalyst and *t*-butyl methyl ether as the solvent in acetylation of diol **13**. The relatively low yield of the desired monoacetates may be due to the formation of byproducts (vide supra). Some attempts to improve the results, using increased amounts of enzymes, did not lead to the expected better outcome.

The comparison of the above results with those obtained in our previous paper devoted to the desymmetrisation of the P = O analogs (vide supra and Scheme 2) [8] clearly shows that the replacement of the phosphinyl (P = O) moiety by the phosphino (P-:) one results in a lower stereoselectivity of the reaction and lower yields of the products.

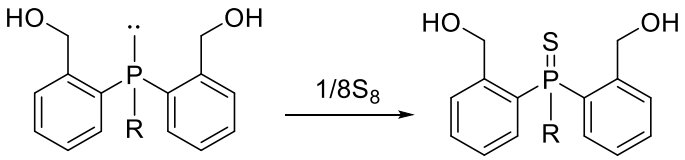
2.3. Desymmetrisation of Bis (2-hydroxymethylphenyl)phosphine Sulfides

Because the results obtained during desymmetrisation of bis (2-hydroxymethyl-phenyl) phosphines **12** and **13** were acceptable, but not very satisfactory and, moreover, some byproducts arising from oxidation phosphines were formed, we decided to synthesize appropriate phosphine sulfides **22** and **23**. Prochiral bis (2-hydroxymethylphenyl)phosphines **12** and **13** were treated with elemental sulfur to give the appropriate phosphine sulfides **22** and **23** (Scheme 5).

Table 1. Monoacetates **14** and **15** via Desymmetrisation of bis (2-hydroxymethylphenyl)phosphines **12** and **13**.

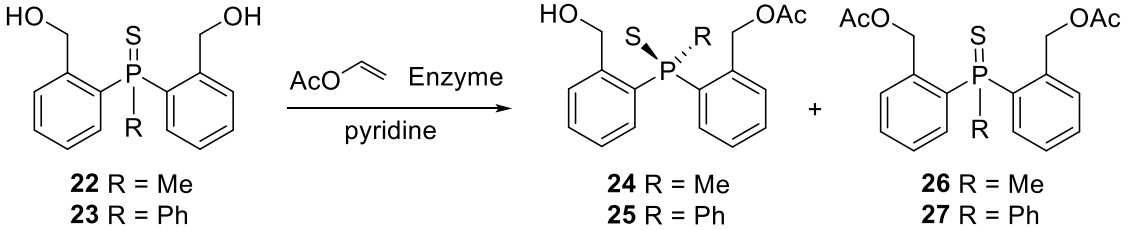
Entry	Diol	R	Enzyme [(a)]	Solvent	Time	Monoacetate			
					[Days]	Symbol	Yield [%]	$[\alpha]_D$ [(b)]	Ee [%] [(c)]
1	**12**	Me	CAL-B	CH_2Cl_2	8	**14**	53	−5.40	40
2	**12**	Me	CAL-B	*i*-Pr_2O	1	**14**	52	−7.10	53
3	**12**	Me	CAL-B	TBME	1	**14**	49	−8.70	64
4	**12**	Me	CAL-B	toluene	11	**14**	25	−9.85	73
5	**13**	Ph	CAL-B	TBME + pyridine	21	**15**	10	4.49	98
6	**13**	Ph	CAL-B	*i*-Pr_2O + toluene + pyridine	23	**15**	10	4.42	95
7	**13**	Ph	CAL-B	acetone	14	**15**	52	2.74	60
8	**13**	Ph	CAL-B	toluene + pyridine	15	**15**	38	2.74	60
9	**13**	Ph	CAL-B	toluene	6	**15**	27	2.28	50
10	**13**	Ph	CAL-B	acetonitrile	22	**15**	26	1.26	28
11	**13**	Ph	CAL-B	$CHCl_3$	12	**15**	16	−1.50	33
12	**13**	Ph	CAL-B	CH_2Cl_2	29	**15**	5	−1.40	31
13	**13**	Ph	PFL	$CHCl_3$	12	**15**	6	−2.26	49
14	**13**	Ph	LPL	toluene	28	**15**	<5	-	-
15	**13**	Ph	CR	toluene	33	**15**	11	2.54	56
16	**13**	Ph	PS	$CHCl_3$	29	**15**	10	-	-
17	**13**	Ph	-	Toluene	24	-	-	-	-

[(a)] Enzyme: CAL-B: *Candida antarctica* lipase B (Novozym 435); PFL: lipase from *Pseudomonas fluorescens*; CR: lipase from *Candida rugosa;* PS: Lipase PS (AMANO); LPL: Lipoprotein lipase; [(b)] in chloroform (c = 1); [(c)] the *ee* values were determined by chiral HPLC: OD, *n*-Hexane: (*i*-PrOH: EtOH 4:1) 98%: 2%, Fl. 0.5 mL/min.



Scheme 5. Synthesis of bis (2-hydroxymethylphenyl)phosphine sulfides **22** and **23**.

The latter were subjected to asymmetric acetylation with an excess of vinyl acetate in various solvents at 30 °C, using a number of lipases (Scheme 6).



Scheme 6. Desymmetrisation of bis (2-hydroxymethylphenyl)phosphine sulfides **22** and **23**.

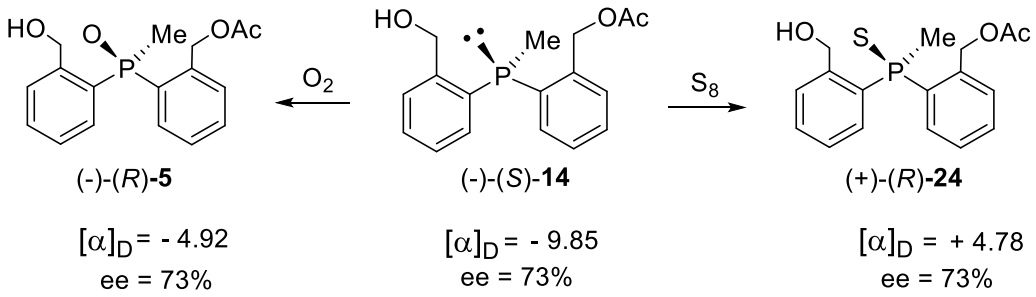
The reactions were monitored by ^{31}P NMR. After completion, the enzymes were filtered off, the solvent and excess of vinyl acetate were evaporated, and the residue was

separated via column chromatography. Interestingly, also in this case, the formation of achiral diacetates **26** and **27** was observed, which, in some cases, may be responsible for a decreased yield of monoacetates. The results are collected in Table 2.

Table 2. Monoacetates **24** and **25** via desymmetrisation of bis (2-hydroxymethylphenyl)phosphine sulfides **22** and **23**.

Entry	Diol	R	Enzyme [a]	Solvent + Pyridine	Time	Monoacetate			
					[Days]	Symbol	Yield [%]	$[\alpha]_D$ [c]	Ee [%] [d]
1	**22**	Me	CAL-B	TBME [b]	4	**24**	60	4.7	72 [e]
2	**22**	Me	CAL-B	toluene	4	**24**	80	3.25	50 [e]
3	**22**	Me	CAL-B	acetone	4	**24**	70	1.65	25 [e]
4	**22**	Me	CAL-B	CH_2Cl_2	8	**24**	49	0	0
5	**22**	Me	CR	TBME	11	**24**	55	0	0
6	**22**	Me	PFL	TBME	11	**24**	60	0	0
7	**23**	Ph	PFL	TBME	38	**25**	60	−7.57	77
8	**23**	Ph	PFL	Et_2O	38	**25**	55	−4.44	45
9	**23**	Ph	PFL	toluene	38	**25**	66	−1.56	16
10	**23**	Ph	PFL	CH_2Cl_2	38	**25**	44	−1.62	16
11	**23**	Ph	CAL-B	Et_2O	38	**25**	44	3.25	54
12	**23**	Ph	CAL-B	i-Pr_2O	38	**25**	37	1.1	0
13	**23**	Ph	CAL-B	acetone	38	**25**	14	2.25	23
14	**23**	Ph	CAL-B	toluene	26		only substrate		
15	**23**	Ph	CAL-B	TBME	16	**25**	10	2.2	23
16	**23**	Ph	CR	TBME	38	**25**	23	1.8	18

[a] Enzyme: CAL-B: *Candida antarctica* lipase B (Novozym 435); PFL: lipase from *Pseudomonas fluorescens*; CR: lipase from *Candida rugose;* [b] TBME: *t*-butyl methyl ether; [c] in chloroform (*c* = 1); [d] the *ee* values were determined by chiral HPLC: AS, *n*-Hexane: (*i*-PrOH: EtOH 4:1) 96%: 4%, Fl. 0.4 mL/min; [e] the ee values were calculated on the basis of the optical rotation, compared to the one shown in Scheme 7 (vide infra).



Scheme 7. Chemical correlation of the absolute configuration of **14** and **24.**

The inspection of Table 2 clearly shows that the reaction time, yields and enantioselectivity strongly depended on the lipase and the solvent used. Monoacetate **24** was obtained in good yield, but with moderate enantioselectivity. In turn, monoacetate **25** was formed in good yield and enantioselectivity. The best results were obtained using PFL as the biocatalyst and *t*-butyl methyl ether as the solvent. Again, attempts to use increased amounts of enzymes did not lead to higher outcomes. Nevertheless, it should be stressed that in both cases presented above, the stereoselective enzymatic transformation was achieved using the substrates in which the prostereogenic phosphorus atom and the reacting hydroxy oxygen were distant from each other by four bonds.

2.4. Determination of the Absolute Configuration of Monoacetates **14** *and* **24**

The absolute configuration of the newly obtained enantiomerically enriched monoacetates was determined as follows: phosphine **14** (Table 1, entry 4) was oxidized with air to give phosphine oxide (-)-(*R*)-**5**, whose absolute configuration and optical rotation are known from our previous work [8]. Since oxidation with air proceeds with the retention of the configuration at phosphorus [15], (*S*) configuration was ascribed to (-)-phosphine **14** obtained. In turn, the reaction of phosphine **14** with elemental sulfur, proceeding also with retention of configuration at phosphorus [15], gave phosphine sulfide **24**. Hence, the absolute configuration of the latter is (+)-(*R*) (Scheme 7), that is, the same as the one obtained in the enzymatic desymmetrisation.

Unfortunately, no such correlation could be made for phosphine monoacetate **15** and phosphine sulfide acetate **25** due to the lack of the corresponding phosphine oxides of known absolute configuration. Moreover, all the chiral products were oils, which excluded X-ray analysis.

3. Materials and Methods

3.1. General Information

The synthesized products were purified by column chromatography on Merck 60 silica gel (0.063–0.200 mm) or preparative plate chromatography using Merck 60 F_{254} silica gel plate (2.5 mm). TLC was performed on Merck 60 F_{254} silica gel plate (0.25 mm). Solvents were dried using general procedures and distilled prior to use. The NMR spectra were recorded in $CDCl_3$ with a Bruker AV 200 spectrometer. The chemical shifts (δ) are expressed in ppm, the coupling constants (*J*) are given in Hz. Mass spectra were recorded with a Finnigan MAT95 Voyager Elite spectrometer or Synapt G2-S*i* mass spectrometer (Waters) equipped with an ESI source and quadrupole-time-of-Flight mass analyser. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. HPLC analysis was made using Varian Pro Star 210 instrument using column with chiral filling Chiralcel OD or Chiralpak AS. The enzymes were purchased from AMANO or SIGMA. Enzymes: CAL-B (Novozym 435)–lipase acrylic resin from *Candida antarctica* (E.C. 3.1.1.3), SIGMA-ALDRICH; PFL–lipase from *Pseudomonas fluorescens* (E.C. 3.1.1.3), SIGMA-ALDRICH; PS–lipase from *Pseudomonas species* (E.C. 3.1.1.3), AMANO, CR–lipase from *Candida rugosa* (E.C. 3.1.1.3), SIGMA-ALDRICH; LPL–Lipoprotein lipase (E.C. 3.1.1.34), SIGMA-ALDRICH. All the NMR spectra are collected in the "Supplementary Materials".

3.2. Synthesis of Bis (2-hydroxymethylphenyl)phosphines **12** *and* **13**

3.2.1. Synthesis of Bis [2-(2′-tetrahydropyranyloxy)methylphenyl]phosphine **10** and **11**

To magnesium (0.264 g, 0.01 mol) under nitrogen was added a solution of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene **7,** obtained according to the known procedure [8] (3 g, 0.01 mol) in THF (8 mL) followed by a small crystal of iodine. The mixture was gently heated to initiate the Grignard reagent formation. After the magnesium completely dissolved, appropriate dichlorophosphine **8** or **9** (0.649 g for **8** or 0.985 g for **9**, 0.0055 mol) dissolved in THF (5 mL) was added and the solution was stirred for 3 h. THF was evaporated, saturated aqueous solution of NH_4Cl (10 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed to give crude phosphine **10** or **11**.

Bis [2-(2′-tetrahydropyranyloxy)methylphenyl]methylphosphine 10
Crude yield: 1.970 g, 90%
^{31}P NMR ($CDCl_3$): δ = −48.3
Bis [2-(2′-tetrahydropyranyloxy)methylphenyl]phenylphosphine 11
Crude yield: 2.535 g, 94%
^{31}P NMR ($CDCl_3$): δ = −25.7

3.2.2. Synthesis of Bis (2-hydroxymethylphenyl)phosphines **12** and **13**

To a solution of crude phosphine **10** or **11** (0.0054 mol) in EtOH (40 mL) pyridinium *p*-toluenesulfonate (PPTS) (0.2 eq., 0.27 g, 0.0011 mol) was added and the mixture was stirred at 55 ºC for 7 h. EtOH was evaporated, to the residue saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After the evaporation of the solvent, the crude products were purified by column chromatography using dichloromethane-acetone in a gradient from 5:1 to 1:1 as eluent to give products **12** and **13**, respectively.

Bis (2-hydroxymethylphenyl)methylphosphine 12
Oil, isolated yield: 0.439 g, 25%
^{31}P NMR ($CDCl_3$): δ = −50.8;
^{1}H NMR ($CDCl_3$): δ = 1.59 (d, *J* = 3.8 Hz, 3H), 4.67–4.90 (m, 4H), 7.27–7.39 (m, 8H);
MS (+ESI): m/z = 261 (M + H);
HRMS (+ESI): m/z = 261.1049, calcd for $C_{15}H_{18}PO_2$ (M + H), 261.1044.
Bis (2-hydroxymethylphenyl)phenylphosphine 13
Oil, isolated yield: 0.098 g, 56%
^{31}P NMR ($CDCl_3$): δ = −27.5;
^{1}H NMR ($CDCl_3$): δ = 4.75–5.04 (m, 4H), 6.94–7.52 (m, 13H);
MS (+ESI): m/z = 323 (M + H);
HRMS (+ESI): m/z = 323.1208, calcd for $C_{20}H_{20}PO_2$ (M + H), 323.1201.

3.3. Synthesis of Bis (2-hydroxymethylphenyl)phosphine Sulfides **22** *and* **23**

To obtain bis(2-hydroxymethylphenyl)phosphine sulfides **22** and **23**, to the solution of phosphine **12** and **13** (0.180 g, 0.692 mmol for **12** and 0.134 g, 0.416 mmol for **13**) in dichloromethane (20 mL) under nitrogen elemental sulfur (1 eq., 0.022 g, 0.692 mmol for **12** and 0.014 g, 0.416 mmol for **13**) was added. The mixture was refluxed until the substrate disappeared, which was found by ^{31}P NMR. Then, the reaction mixture was filtered through celite and the solvent was evaporated. The crude reaction mixture was purified by column chromatography using dichloromethane-acetone 6:1 with the addition of triethylamine (0.03% vol.) to give pure **22** and **23**.

Bis (2-hydroxymethylphenyl)methylphosphine sulfide 22
Yellowish solid, m. p. 92–94 °C, isolated yield: 0.124 g, 61%
^{31}P NMR ($CDCl_3$): δ = 34.2;
^{1}H NMR ($CDCl_3$): δ = 2.34 (d, J = 13.2 Hz, 3H), 3.71 (br. s, 1H), 4.39–4.75 (m, 4H), 7.11–7.72 (m, 8H);
^{13}C NMR ($CDCl_3$): δ = 23.68 (d, $J_{P\text{-}Me}$ = 60.5 Hz), 62.93 (d, $J_{P\text{-}CH2OH}$ = 6.0 Hz), 128.15, 131.03, 131.12, 131.73, 132.22, 132.30, 132.36, 132.74, 143.97, 144.04 (Aryl);
MS (+ESI): m/z = 293 (M + H);
HRMS (+ESI): m/z = 293.0771, calcd for $C_{15}H_{18}PO_2S$ (M + H), 293.0765.
Bis (2-hydroxymethylphenyl)phenylphosphine sulfide 23
Yellowish solid, m. p. 132–134 °C, isolated yield: 0.111 g, 76%
^{31}P NMR ($CDCl_3$): δ = 40.7;
^{1}H NMR ($CDCl_3$): δ = 3.85 (br. s, 1H), 4.67–4.82 (m, 4H), 5.29–5.49 (m, 2H), 6.78–7.72 (m, 13H);
MS (CI): m/z = 355 (M + H);
HRMS (CI): m/z = 354.0845, calcd for $C_{20}H_{19}PO_2S$ (M + H), 354.0843.

3.4. General Procedure for the Enzymatic Desymmetrization of Bis (2-hydroxymethylphenyl)phosphines **12** *and* **13** *and Bis (2-hydroxymethylphenyl)phosphine Sulfides* **22** *and* **23**

To a solution of the prochiral phosphine diol (**12** or **13**, 0.1 mmol) or prochiral *P*-sulfide diol (**22** or **23**, 0.1 mmol) in a solvent (5 mL) pyridine (3 eq., 0.024 mL, 0.3 mmol), vinyl

acetate (0.5 mL) and an enzyme (20 mg) were added. In the case of phosphines **12** and **13**, the reaction was carried out under a nitrogen atmosphere. The whole mixture was stirred at room temperature. The conversion degree was determined by ^{31}P NMR. Then, the enzyme was filtered off and the solvents were evaporated. The crude reaction mixture was separated by column chromatography using dichloromethane-acetone in gradient from 100:1 to 1:1 with the addition of triethylamine (0.03% vol.) as eluent, to give pure enantiomerically enriched phosphine monoacetates **14** and **15** and *P*-sulfide monoacetates **24** and **25**. The results are collected in Table 1 for phosphines **12** and **13** and in Table 2 for sulfides **22** and **23**.

(2-acetoxymethylphenyl)(2′-hydroxymethylphenyl)methylphosphine 14
^{31}P NMR ($CDCl_3$): δ = −48.4;
^{1}H NMR ($CDCl_3$): δ = 1.59 (d, J = 3.6 Hz, 3H), 1.86 (s, 3H), 4.69–4.89 (m, 4H), 7.19–7.48 (m, 8H);
MS (CI): m/z = 303 (M + H);
HRMS (+ESI): m/z = 303.1158, calcd for $C_{17}H_{20}PO_3$ (M + H), 303.1150.
(2-acetoxymethylphenyl)(2′-hydroxymethylphenyl)phenylphosphine 15
^{31}P NMR ($CDCl_3$): δ = −26.3;
^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 3H), 4.71–4.82 (m, 2H), 5.29–5.49 (m, 2H), 6.81–7.44 (m, 13H);
MS (FAB): m/z = 365 (M + H);
HRMS (FAB): m/z = 365.1317, calcd for $C_{22}H_{22}PO_3$ (M + H), 365.1306.
(2-acetoxymethylphenyl)(2′-hydroxymethylphenyl)methylphosphine sulfide 24
^{31}P NMR ($CDCl_3$): δ = 33.7;
^{1}H NMR ($CDCl_3$): δ = 1.89 (s, 3H), 2.38 (d, J = 13.2 Hz, 3H), 4.31–4.75 (m, 2H), 4.94–5.09 (m, 2H), 7.36–8.15 (m, 8H);
MS (+ESI): m/z = 335 (M + H);
HRMS (+ESI): m/z = 335.0876, calcd for $C_{17}H_{20}PO_3S$ (M + H), 335.0871.
(2-acetoxymethylphenyl)(2′-hydroxymethylphenyl)phenylphosphine sulfide 25
^{31}P NMR ($CDCl_3$): δ = 41.2;
^{1}H NMR ($CDCl_3$): δ = 1.84 (s, 3H), 4.01 (br. s, 1H), 4.60–4.82 (m, 2H), 5.38–5.55 (m, 2H), 6.89–7.73 (m, 13H);
MS (CI): m/z = 397 (M + H);
HRMS (+ESI): m/z = 397.1023, calcd for $C_{22}H_{22}PO_3S$ (M + H), 397.1027.

4. Conclusions

Prochiral bis (2-hydroxymethylphenyl) phosphines and their sulfides could be successfully transformed into enantiomerically enriched monoacetyl derivatives by a desymmetrisation procedure using an enzymatic acetylation reaction. The use of enzymes proved to be useful in obtaining the desired products with high stereoselectivity in one step. The determination of their absolute configuration proved that, in the case of phosphines, phosphine oxides and phosphine sulfides enzymes preferentially produce compounds of the same spatial arrangement. The new compounds obtained will be transformed into chiral catalysts/ligands. The appropriate investigations are underway.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12020171/s1: NMR spectra of all the new compounds.

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